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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,081	11/09/2001	Didier Trono	CLFR:010US/TMB	2667
7590	06/18/2004		EXAMINER	
Thomas M. Boyce FULBRIGHT & JAWORSKI L.L.P. SUITE 2400 600 CONGRESS AVENUE AUSTIN, TX 78701			KAUSHAL, SUMESH	
			ART UNIT	PAPER NUMBER
			1636	
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Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

<b>Application No.</b> 10/010,081	<b>Applicant(s)</b> TRONO ET AL.
<b>Examiner</b> Sumesh Kaushal Ph.D.	<b>Art Unit</b> 1636

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) Responsive to communication(s) filed on 31 March 2004.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) Claim(s) 1-37 is/are pending in the application.  
 4a) Of the above claim(s) 11,13-18,20,21 and 24 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-10,12,19,22,23 and 25-37 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 09 November 2001 is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |  |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)<br>2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)<br>3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>3/02, 2/03, 2/03</u> . | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____.<br>5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)<br>6) <input type="checkbox"/> Other: _____. |
|--|--|

### **DETAILED ACTION**

Applicant's response filed on 03/31/04 has been acknowledged.

Claims 1-37 are pending.

Claims 11, 13-18, 20-21, 24 are withdrawn by applicant.

Claims 1-10, 12, 19, 22-23, 25-37 are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

#### ***Election/Restrictions***

Applicant's election without traverse of Claims 1-10, 12, 19, 22-23, 25-37, wherein the elected species are EF-1 $\alpha$  promoter, the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) and multi drug resistance gene in the reply filed on 03/31/04 is acknowledged.

Claims 11, 13-18, 20-21 and, 24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/27/04.

#### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

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1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 19, 22-23, 25-26, 29-37 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 69, 82-84, 97-99, 107, 110-111, 113-121 of copending Application No. 10/261,078. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of lentiviral transfer vector, transduced host cells and the method of transducing human hematopoietic stem cells as claimed in the 10/261,078 encompasses the self inactivating recombinant vector, host cells and method of transducing human hematopoietic stem cells as claimed in instant application (10/010,081).

Specifically the scope of claims 69, 82-84 of '078 are drawn to a self-inactivating lentiviral vector (SIN), wherein the LTR region has been rendered inactive is identical to the scope of claims 1 and 31 of instant application. Similarly the scope of claims 97-99 of '078 encompasses a lentiviral vector, wherein the promoter is capable of promoting expression of the transgene in the range of 10-200 is identical to the scope of the invention of claims 6-8 of instant application. Furthermore the scope of lentiviral vector of claims 107 and 110-111 of '078 encompasses the lentiviral vector comprising WPRE, which is identical to the claims 19 and 22-23 of instant application. Furthermore the scope of host cell of claims 113-115 of '078 is identical to the host cells (hematopoietic progenitor cells) of claims 26 and 29-30 of instant application. In addition the scope of method of transducing human hematopoietic stem in claims 116-121 of '078 is identical

to claims 32-37 of instant application. Thus the invention as claimed in the '078 and the instant application are obvious in view of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-10, 19, 22-23, 25-36 are rejected under 35 U.S.C. 102(a) as being anticipated by Ramezani et al (Mol. Ther. 2(5): 458-469, 2000, ref of record on PTO-1449).

Regarding claims 1-5 and 31 the cited art teaches a self-inactivating SIN lentiviral vector based on the pHR' vector system derived from HIV-1 backbone, which inherently contains *gag*, *pol* and *env* genes (page 459, col1, para.1, col.2 para.2, see Zufferey et al J. Virol 72(12): 9873, 1998, ref of record on PTO -1449). The cited art further teaches that the SIN vector contains a deletion (-418 to -18 relative to U3/R boundary) in the U3 region of 3'LTR. The cited art further teaches a SIN lentivrial vector, wherein the transgene (GFP) is positioned under the control of EF1- $\alpha$  promoter (page 461, fig-1, SIN-EF-GFP-W).

Regarding claims 6-8 and 31 the cited art teaches that the EF1-a promoter derives the expression of GFP in human hematopoietic progenitors cells at a signal to noise ratio between about 10 and about 200 (page 464, fig-4 EF1- $\alpha$  promoter; page 466 fig-7, EF-GW). Since the signal to noise ratio is an arbitrary value, given the broadest reasonable interpretation the data presented in fig-7 (EF-GW) clearly anticipate the claimed signal to noise ratio. In addition, the cited art clearly anticipate the invention as

claimed because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02.

Regarding claim 9 and 10 the cited art teaches that the EF1a promoter is a strong promoter that is active to promote detectable expression of a transgene in primary human CD34+ hematopoietic stem cell/progenitor cells (HSPCs) see page 459, col.1, para. 2).

Regarding claim 19, 22 and 23 the cited art teaches a HIV- based SIN lentiviral vector comprising the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). The cited art further teaches a SIN lentiviral vector containing WPRE, wherein the transgene (GFP) is positioned under the control of EF1-a promoter (page 461, fig-1, SIN-EF-GFP-W) and is further regulated by WPRE (page 461, fig-1, SIN-EF-GFP-W).

Regarding claims 25 the cited art teaches that the SIN lentiviral vector derived from HIV-1 contains a deletion (-418 to -18 relative to U3/R boundary) in the U3 region of 3'LTR (page 459, col.1 para.2).

Regarding claims 26-28 the cited art teaches transduction of the 293T virus producing host cells with SIN lentiviral vector (page 463 col.1 para.2).

Regarding claim 29-30, 32-36 the cited art teaches transduction of CD34+, KG1a and cord blood progenitors cells with SIN lentiviral vector (Page 464, col.1 para.2, page 466 col.1, para.2). The cited art further teaches culture conditions that stimulate proliferation of hematopoietic progenitor cell, wherein 75% of the cells retained the CD34+ phenotype after 6 days of cell culture (page 466 fig-7). The cited art further teaches the infusion of genetically modified hematopoietic stem cells in a NOD/SCID and SCID-hu mice models (page 466, col.2 para.1; page 468, para. 2).

Thus the cited art clearly anticipate the invention as claimed.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Zufferey et al (J. Virol. 72(912):9873-9880, 1998, ref. of record on PTO-1449).

The instant claims are drawn to a self-inactivating (SIN) recombinant vector comprising lentiviral gag, pol and rev genes, a promoter that is active in human hematopoietic progenitor cells and an LTR region with reduced promoter activity relative to wild-type LTR.

Zufferey teaches self-inactivating HIV-1 based lentivirus vector (SIN) comprising the HIV-1 back bone containing HIV-1 gag, pol and rev genes (page 9873, abstract, col.2 para.1; page 9874, col.1 paras 3-7). The cited art further teaches that the SIN vectors contains a 400-nucleotide deletion in the 3' LTR which renders the LTR inactive as compared to wild type LTR (page 9874, col.2 para.5, page 9875, table-1, page 9876, table-2, page 9877 table-3). The cited art further teaches that the SIN lentiviral vector comprises the CMV internal promoter, wherein the CMV promoter is inherently known to promote detectable transcription of a transgene in human hematopoietic progenitor cells (see Case et al PNAS 96:2988-2993, 1999, ref. of record on PTO-1449).

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

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invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 12 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramezani et al (Mol. Ther. 2(5): 458-469, 2000, ref of record on PTO-1449) as applied to claims 1-10, 19, 22-23 and 25-36 above, and further in view of Deisseroth (Clinical Cancer Research 5: 1607-1609, 1999).

Ramezani et al teaches a self-inactivating SIN lentiviral vector comprising the EF1- $\alpha$  promoter that derives the expression of a transgene in human hematopoietic cell and a deletion in U3 region of the LTR (*supra*).

However the cited art does not teach a self-inactivating SIN lentiviral vector wherein the transgene is a multidrug resistance gene (MDR). In addition the cited art does not teach that the infusion of transduced stem cell into a human subject.

Deisseroth teaches clinical trials involving multidrug resistance transcription units encoded in retroviral vectors. The cited art teaches the use of retroviral vectors to transfer human MDR-1 into human hematopoietic cells in vitro (page 1607, col. 1 para 4; col. 2 para.2). The cited art further teaches clinical trials, which show engraftment of vector modified clonogenic hematopoietic progenitor cells into human patients (page 1608, col.1). The cited art further teaches the use of lentiviral vectors to transduce early hematopoietic stem cells, which resulted in the transduction of at least 80% of CD34+/CD38- hematopoietic stem cells (page 1608, col.2 para.d).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Ramezani by substituting the GFP reporter gene with a MDR gene in view of Deisseroth. One would have been motivated to do so, since the transduction of human hematopoietic progenitor cells with the MDR-gene decrease the toxicity of chemotherapeutic agents in hematopoietic cells. One would have a reasonable expectation of success in doing so, since retrovirus induced transduction of human progenitor cells (to express a gene of interest) has been routine in the art at the time of instant invention. In addition one would have been motivated to infuse genetically modified hematopoietic stem cells into a human subject to show engraftment

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and clonogenic potential of genetically marked hematopoietic progenitor cells. One would have a reasonable expectation of success in doing so, since the transplantation of progenitor cells especially in patients undergoing chemotherapy has been routine in the art at the time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Claims 6-10 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72(9):9873-9880, 1998, ref. of record on PTO-1449) as applied to claims 1-5 above, and further in view of Chang et al (Gene Therapy 6:715-728, 1999).

Zufferey teaches self-inactivating HIV-1 based lentivirus vector (SIN) comprising the HIV-1 back bone containing HIV-1 gag, pol and rev genes (page 9873, abstract, col.2 para.1; page 9874, col.1 paras 3-7). The cited art further teaches that the SIN vectors contains a 400-nucleotide deletion in the 3' LTR which renders the LTR inactive as compared to wild type LTR (page 9874, col.2 para.5, page 9875, table-1, page 9876, table-2, page 9877 table-3). The cited art further teaches that the SIN lentiviral vector comprises the CMV internal promoter, wherein the CMV promoter is inherently known to promote detectable transcription of a transgene in human hematopoietic progenitor cells (see Case et al PNAS 96:2988-2993, 1999, ref. of record on PTO-1449).

Even though Zufferey teaches a self-inactivating HIV-1 based lentivirus vector, the cited art dose not teach a lentiviral vector, wherein the EF-1 $\alpha$  promoter directs the expression of a transgene.

Regadng claims 9-10 specifically, Chang teaches a HIV-1 derived vector system comprising pTV $\Delta$ EFGPF genetic construct, which comprises human elongation factor 1 $\alpha$  promoter (page 126, col.1 para.1, line 21-26). The cited art further teaches the transduction of human CD34+ hematopoietic stem cells using pTV $\Delta$ EFGPF lentiviral vector, wherein the transduced progenitor cells express the GFP transgene under the

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control of the human elongation factor 1 $\alpha$  promoter (page 718, col.2 para. 2; page 723, fig-5).

Regarding claims 6-8 and 31 the cited art teaches that human hematopoietic progenitor cells express the GFP transgene expression under the control of an EF-1 $\alpha$  promoter, wherein the signal to noise ratio of the expressed GFP falls with the range of about 10 and about 200 (page 723, fig-5 see inset a-d). The cited art disclose that the phase contrast microscopy reveled that the strength of GFP signal is significantly higher than the untransduced colony (inset-a, lower colony). Such a contrast certainly fall in the range of signal to noise ratio as claimed (between about 10 and about 200). The signal to noise ratio is an arbitrary value that not only depends upon the strength of transgene signal by is also a function of instrument sensitivity and settings. Therefore the cited art clearly teaches that the EF-1 $\alpha$  promoter provides transgene expression with higher signal to noise ratio in human hematopoietic progenitor cells. In addition, the cited art clearly anticipate the invention as claimed because the composition and functions as claimed are presumed inherent. The composition is physically the same it must have the same properties. "Products of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990) see MPEP § 2112.02.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the self-inactivating HIV-1 based lentivirus vector of Zufferey by substituting the CMV promoter with human elongation factor 1 $\alpha$  promoter. One would have been motivated to do so because the EF-1 $\alpha$  promoter is strong promoter to regulate the expression of a transgene in primary CD34+ hematopoietic stem cells. One would have a reasonable expectation of success of success in doing so, since substituting a promoter sequence with another has been routine in at time of instant invention. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

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Claims 19, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zufferey et al (J. Virol. 72(912):9873-9880, 1998, ref. of record on PTO-1449).as applied to claims 1-5 above, and further in view of Zufferey et al (J. Virol. 73(4):2886-2892, 1999, ref. of record on PTO-1449).

Zufferey teaches self-inactivating HIV-1 based lentivirus vector (SIN) comprising the HIV-1 back bone containing HIV-1 gag, pol and rev genes (page 9873, abstract, col.2 para.1; page 9874, col.1 paras 3-7). The cited art further teaches that the SIN vectors contains a 400-nucleotide deletion in the 3' LTR which renders the LTR inactive as compared to wild type LTR (page 9874, col.2 para.5, page 9875, table-1, page 9876, table-2, page 9877 table-3). The cited art further teaches that the SIN lentiviral vector comprises the CMV internal promoter, wherein the CMV promoter is inherently known to promote detectable transcription of a transgene in human hematopoietic progenitor cells (see Case et al PNAS 96:2988-2993, 1999, ref. of record on PTO-1449).

However Zufferey-1998 does not teach SIN vector comprising the virus posttranscriptional regulatory element that promote the expression of a transgene, wherein the posttranscriptional regulatory element is woodchuck hepatitis virus posttranscriptional regulatory element (WPRE).

Zufferey-1999 teaches a HIV-1 based retroviral vector (pHR' CMV-GFP) that contains woodchuck hepatitis virus posttranscriptional regulatory element (WPRE). see page 2887 fig-1A, col.2 para. 2). The cited art further teaches that WPRE enhances the expression of a transgene in host cells transduced by the HIV-based vectors (page 2888, fig-2, col.2 results).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Zefferey-1998 by incorporating posttranscriptional regulatory element obtained from woodchuck hepatitis virus posttranscriptional regulatory element (WPRE) in view of Zufferey-1999. One would have been motivated to do so to increase the levels of expression of a transgene in host cells. One would have a reasonable expectation of success in doing so, since genetic modification of lentiviral vectors has been routine in the art at time the instant invention was made. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for transducing isolated human hematopoietic stem cells (in-vitro), does not reasonably provide enablement for a method for transducing human hematopoietic stem cells in-vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

**Nature of Invention:**

The instant invention encompasses a method for in-vivo gene therapy.

**Breadth of Claims and Guidance Provided in the Specification**

The scope of invention as claimed encompasses a method for transducing human hematopoietic stem cells in-vivo. At best the specification (as filed) teaches transduction of isolated hematopoietic stem cell in-vitro (spec. example-1 and 2). The specification fails to disclose that the administration of the self-inactivating viral vector via any and all routes of administration would lead to the transduction of human hematopoietic progenitor cells in-vivo.

**State Of Art And Predictability:**

The scope of the instant invention encompass a cell transduced in-vivo therefore the instant invention as claimed reads upon method that falls in the realm of gene therapy. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Juengst BMJ, 326:1410-11, 2003, Anderson WF, Nature 392:25-30, 1998). It has been difficult to predict the efficiency and outcome of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells

represents the first critical step in gene delivery, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors. Furthermore, in-vitro gene transfer studies are not predictive of in-vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are undergoing rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in-vivo is still one of the most difficult obstacles to overcome. The viral particles binds to many cells they encounter in vivo and therefore would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). The instant specification fails to provide any guidance, which enables one skill in the art to selectively target small number of hematopoietic stem cells that exists in-vivo.

In instant case transduction of hematopoietic progenitor cell in-vivo via any and all means (systemic or local) is not considered routine in the art and without sufficient guidance the method (as claimed) the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and the insufficient amount of guidance provided in the instant specification as filed one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-10 and 29-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-8 and 31 are indefinite because instant claim recites claim limitation "about" to describe the signal-to-noise ratio (i.e. between about 10 and about 200). "About" means *reasonably close or in the vicinity*. Since "about" does not defines the exact starting position of the value as claimed, the terminology does point out the subject matter which applicant regards as the invention. For example it is unclear whether the value of signal-to-noise ratio of 10 is excluded or included in this context.

Claim 29 is indefinite because human hematopoietic progenitor cells (primary cells) are not related to 293T cells, which is an immortalized fibroblast cell line derived from human embryonic kidney cell. Changing the dependency of instant claim to "claim 26" has been suggested.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: "conditions to effect the transduction of human hematopoietic progenitor cell". For example it is unclear whether the conditions in this context include any specialized growth media, treating the vector with any reagent to enhance binding or any physical treatment of cells that would effect the transduction of human hematopoietic progenitor cells exclusively.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or

Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal  
Examiner GAU 1636



**SUMESH KAUSHAL**  
**PATENT EXAMINER**